13

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,549	03/29/2004	You-Di Liao	16743-004001 / 12A-921112	4099

26181 7590 12/21/2005

FISH & RICHARDSON P.C.
PO BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
MOORE, WILLIAM W	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 12/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/813,549	LIAO, YOU-DI	
	Examiner	Art Unit	
	William W. Moore	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-34* is/are pending in the application.

4a) Of the above claim(s) *17-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16 and 24-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20040526*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

The instant application enjoys the priority of its 29 March 2004 filing date in the United States.

Information Disclosure Statement

Applicant's Information Disclosure Statement [IDS] filed on 26 May 2004 is hereby acknowledged.

Preliminary Amendment

Applicant's Preliminary Amendment filed on 17 August 2004, has been entered, revising Tables 3 and 4 at pages 28 and 32 of the specification and supplying a sequence listing in both printed and computer readable forms.

Election

Applicant's election without traverse of the invention of Group II, claims 9-16, in the reply filed 7 October 2005 is acknowledged. Applicant cancels claims 1-8 and adds the new claims 24-34 which correspond to the subject matter of the elected Group II. Thus claims 9-34 remain in the application of which claims 17-23 corresponding to the non-elected Group III are withdrawn from consideration as drawn to a non-elected invention.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:
Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9-13 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claim 9 does not describe a "new . . . composition of matter" as required by the statute because mere recitation of the phrase "comprising a polypeptide that comprises an engineered version of SEQ ID NO:1" fails to distinguish a cell that is present in

Nature in its native state, where the "engineering" is not achieved by the efforts of a person and instead occurs due to random mutation in a chromosomal DNA sequence, from a cell of, e.g., claim 16, wherein an engineered polypeptide is present in a cell only when a person has designed and prepared a DNA molecule and transformed the cell with the DNA molecule. Claims 10-13 are included in the rejection where they depend from claim 9 but do not otherwise describe statutory subject matter. This rejection may be overcome by amending claim 9 to recite "[a]n **isolated** cell".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-16 and 24-34 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the preparation of the divergent methionine aminopeptidase within the cell described by claim 9 and the preparation of a DNA molecule encoding the divergent methionine aminopeptidase of claim 14. It is agreed that the specification discloses the preparation of DNA molecules encoding the amino acid sequences of modified *E. coli* methionine aminopeptidases wherein the substitutions required at either or both of positions 206 and 233 in SEQ ID NO:1 recited in claims 9, 14, and 24-27 are made, as well as further modified *E. coli* methionine aminopeptidases wherein the additional substitutions at position 168 in SEQ ID NO:1 recited in claims 28-31 are made. The specification even discloses, in paragraph 71 at page 12, other amino acid substitutions not required at any position in SEQ ID NO:1 recited in the claims, teaching both prior art amino acid sequence alterations that can be

tolerated in the region of the substrate binding region of the methionine aminopeptidase of SEQ ID NO:1 as well as prior art amino acid sequence alterations near the substrate binding region of the methionine aminopeptidase of SEQ ID NO:1 that are deleterious to its catalytic activity.

In reciting "a polypeptide that comprises an engineered . . . SEQ ID NO:1", claims 14 and 19 reach a myriad of undisclosed, generic, proteins, however, that need not function as methionine aminopeptidases and that may differ by amino acid deletions, substitutions, and/or insertions at any number of the non-recited positions in the amino acid sequence of SEQ ID NO:1. While this may not be Applicant's intent, the claims and the specification fail to describe where the differences occur at unrecited amino acid positions in the polypeptide and fail to describe what the differences might be, nor does the specification otherwise disclose or suggest the nature or source of any of the generic proteins that meet the few limitations of the claims. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification furnishes no relevant identifying characteristics of polypeptides that have no particular function yet diverge at an unknown number of amino acid positions from the sequence of SEQ ID NO:1, nor does it provide any characteristic permitting a correlation between structures of these undisclosed structures of polypeptides among the generic polypeptides present in a cell of claim 9, or encoded by a DNA molecule of claim 14, and the disclosed amino acid sequences of SEQ ID NO:1. Claims 10-13, 15, 16, and 24-34 are included in this rejection because they depend from claims 9 and 14 and also fail to define a genus of polypeptide structures supported by the disclosure of the specification. This rejection

may be overcome with respect to all elected claims by amending claims 9 and 14 to require that a polypeptide have methionine aminopeptidase activity and to require a close structural relationship between the engineered product and the starting product such as those described at page 9, lines 32 and 33, of the specification (at least 95% identical) or at page 13, lines 5 and 6, of the specification (no more than 5 other point mutations in SEQ ID NO:1).

Claims 9-16 and 24-34 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the preparation of , does not reasonably provide enablement for . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to [practice a method of] [make] [make and use] the invention commensurate in scope with these claims.

Claims 9 and 14 contemplate an arbitrary assignment of any or all of amino acid substitutions, additions or deletions within the primary structure of SEQ ID NO:1 and do not require that a modified product have any particular function, even the disclosed function of the starting product before modification. Although the specification teaches a number of amino acid substitutions at particular positions, and combinations thereof, that will advantageously increase the range of substrates cleaved by the *E. coli* methionine aminopeptidase of SEQ ID NO:1, this rejection is stated under the first paragraph of the statute because the specification cannot support introduction of an unknown number of amino acid sequence alterations in the amino acid sequence of SEQ ID NO:1 that are amino acid insertions, deletions, or substitutions anywhere, in any combination or any pattern, in the amino acid sequence set forth, respectively, in SEQ ID NO:1. Indeed, the prior art made of record herewith taken together with Applicant's specification identifies but fourteen amino acid positions in the sequence set forth in SEQ ID N:1 where amino acid substitutions, of which two positions at two positions severely limit the function of the methionine aminopeptidase. Mere sequence perturbation cannot enable the design and preparation of nucleotide sequences

encoding a myriad of divergent polypeptides and provide the public with a nucleotide sequence encoding an methionine aminopeptidase that retains its native function..

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (discussing eight factors relevant to analysis of enablement). Applying the factors discussed in *Wands*, ***supra***, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering the amino acid sequence of SEQ ID NO:1 at any number of positions to the extent permitted by the claims,

b) the specification lacks working examples wherein the amino acid sequence of SEQ ID NO:1 is altered at any position to the extent permitted by the claims,,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no members of the class of methionine aminopeptidases represented by amino acid sequences of SEQ ID NO:1 have had as many as three amino acid positions specifically identified for concurrent modification.

Thus the scope of subject matters embraced by claims 9 and 14 is unsupported by the present specification even if taken in combination with teachings available in the prior art. Claims 10-13, 15, 16, and 24-34 are included in this rejection because they depend from claims 9 and 14 and also fail to define a genus of polypeptide structures supported by the disclosure of the specification. This rejection may be overcome by amending claims 9 and 14 to require that an engineered polypeptide have methionine aminopeptidase activity and to require a close structural relationship between the engineered product and the starting product such as those described at page 9, lines 32 and 33, of the specification (at least 95% identical) or at page 13, lines 5 and 6, of the specification (no more than 5 other point mutations in SEQ ID NO:1).

Allowable Subject Matter

While subject to rejections above under 35 U.S.C. §§ 101 and 112, first paragraph, DNA molecules encoding *E. coli* methionine aminopeptidases modified by substitutions of any of glycine, threonine, aspartate, valine, and asparagine at either or both of the disclosed positions 106 and 233 of SEQ ID NO:1 are free of the prior art of record herein, and expression vectors and host cells comprising such DNA molecules as well as isolated cells comprising such modified *E. coli* methionine aminopeptidases are also free of the prior art of record herein. This is because the closest teaching of alteration of an S'_1 substrate binding pocket – the cavity adjacent to the active site of a methionine aminopeptidase that accepts the penultimate amino acid of an initial translation product from which the methionine is cleaved – at positions equivalent to Met206 and Gln233 in the *Escherichia coli* methionine aminopeptidase amino acid sequence of SEQ ID NO:1 is that of Walker et al., 1999, made of record with Applicant's Information Disclosure Statement filed 26 May 2005. But Walker et al., 1999, teach only the substitution of alanine at the equivalent positions in the cognate yeast methionine aminopeptidase 1 and are silent as to the potential nature and/or benefit of any other substituent that might be used in making a substitution in the binding site at these positions instead of alanine, thus cannot render obvious the amino acids recited in claims 9, 14, 24, 25 and 27 herein. Neither Lowther et al., 1999, nor Lowther et al., 2000, also made of record with Applicant's Information Disclosure Statement fail to teach or suggest any potential substituents for the methionine and glutamine at, respectively, positions 206 and 233 in the amino acid sequence of SEQ ID NO:1 where Lowther et al., 2000, only acknowledge the work of Walker et al., at page 165, and Lowther et al., 1999, only identify the positions 206 and 233 as contributing to the an S'_1 substrate binding pocket, at page 7689. The publication of Nielsen et al., WO 2005/059127 is made of record

herewith as pertinent to Applicant's disclosure but is not prior art to an invention claimed herein because the International Filing Date is nine months later than the US filing date of the instant application, 29 March 2004.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
12 December 2005

NASHAAT T. NASHED PHD.
PRIMARY EXAMINER